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EFFECT OF PASSIVE SMOKING IN LUNG CANCER DEVELOPMENT IN WOMEN IN THE NARA REGION

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Introduction

It is becoming noticeable in Japan that with increased incidence of lung cancer, there has been an increase in pulmonary carcinoma in women. Active smoking by women is increasing, while concern over passive smoking has been intensifying, and the effect of passive smoking on carcinogenesis has become a social problem. Regarding this effect, immunological and public health reports have appeared in Japan, but there have been few clinical reports, and detailed analysis of patients has been inadequate. Lung cancer presents a variegated histological picture, and presumably there are different carcinogenic factors for different histological types, although there have also been few reports on this subject. The effect of passive smoking probably varies depending on the regional environment and custom, and these factors should also be analyzed and included in the investigation. The present report describes our findings regarding the effects of smoking and familial aggregation of cancer in cases of pulmonary carcinoma in women.

1. Subjects and Method

1) Subjects

The subjects were 25 women with lung cancer who were admitted to our department. They averaged 67.5±8.8 years of age. Based on histology there were 7 cases of squamous cell carcinoma, 5 of small cell carcinoma and 13 of adenocarcinoma. The age averages for the above groups were 71.4±7.8, 66.2±9.3 and 65.8±9.0 years, respectively. As controls, 50 cases of non-malignant hospitalized patients matched for sex and age (within 2 years) were selected. Their age average was 67.6±8.5 years.

2) Items of examination

To gather data on active and passive smoking (current and past) and familial accumulation of cancer, detailed questioning was conducted regarding personal history, concomitant disease, exposure to atmospheric pollution, stress, occupation, obesity, alcohol consumption and other items with the patient herself and with the family. Passive smoking was defined as exposure to smoking more or less daily through living with a smoker, and the amount was defined as the number of cigarettes smoked by the smoker each day multiplied by the number of years of exposure. Familial accumulation was based on occurrence or absence of malignancy in relatives to the 3d degree. Comparison with controls was made on the basis of significance of difference and relative risk regarding smoking and familial factors for each histologic type of tumor. Squamous cell carcinoma and small cell carcinoma which are regarded as

having an intimate relation to smoking were grouped together.

2. Results

1) Squamous cell carcinoma (Table 1)

There were 4 patients who were active smokers out of 7. Passive smoking was experienced in all, but 6 were currently exposed while 5 had a history of exposure. Three reported exposure at an early age. Familial accumulation was observed in 4 cases, of which 3 were lung cancer, a high incidence, while 2 were gastric cancer. General history included one case of ovariectomy and 2 cases of ulcer of the digestive tract. Four had experienced atmospheric pollution and 3 reported stress. In the 3 non-smokers (cases 5, 6 and 7), passive smoking and familial cancer both occurred. These patients were the most elderly.

2) Small cell carcinoma (Table 1)

Four of 5 were active smokers. Passive smoking occurred in all 5, these all being exposed currently, while one case had a history of passive smoking and one could not be determined regarding this information. Familial accumulation was found in 4 cases, 3 being cases of gastric cancer, a high incidence. As for personal history, there was one case each of uterine cancer and hysterectomy and one case of breast cancer. Exposure to atmospheric pollution occurred in 2 and stress in 4. In the one non-smoker (case 5) there was intense passive smoking. The individual had a history of surgery for breast cancer, and her two younger sisters had had breast cancer and uterine cancer (individually). This group of patients averaged 5 years younger than the cases of squamous cell carcinoma.

3) Adenocarcinoma (Table 2)

There was not a single active smoker out of 13, but all had been exposed to passive smoking, 12 out of 13 being currently exposed. There were 10 out of 11 who had a history of passive smoking, 8 since early childhood. Familial incidence of cancer was present in 11 out of 13, two being lung cancer, 7 gastric cancer, 4 esophageal cancer and 2 colon cancer. Three had uterine fibroid and 1 had undergone hysterectomy. There were 2 cases of respiratory disease. Exposure to atmospheric pollution occurred in 5, and stress in 4. In 11 out of 13 there was passive smoking along with familial cancer. In the other two there was intense passive smoking in one and passive smoking plus pulmonary tuberculosis in the other.

4) Controlled studies (Tables 3, 4 and 5)

Regarding passive smoking (Table 3), there was a significant difference between lung cancer cases and controls in the amount of exposure ($p<0.05$), although no definite difference could be observed according to tumor cell type. When the cases were grouped into those who had been exposed up to the present time, those who had been exposed in the past and those who had been exposed since early childhood,

Table 1. Squamous cell carcinoma and small cell carcinoma of the lung in women.

A. Squamous cell carcinoma.

	Age	Active smoking	Passive smoking: Past	Passive smoking: Present	Familial cancer	Personal history of disease	Concomitant illness	Air pollution	Occupation	Stress	Others
1. T.O.	78	500	son + 1,600 cigs	father, husb loose tob	—	pyelitis	hyper-tension	+	house-wife	–	husband: gastric ca. TB
2. M.R.	57	853	husb son 1,653 400 cigs	younger bro. loose tob	—	excision of ovary	—	–	house-wife	–	
3. N.O.	70	330	husb 400 cigs	—	Aunt (LC)	Gastric ulcer	Lumbar deforma.	–	house-wife	–	
4. K.S.	70	300	—	father husb loose tob 360 cigs	—	Lumbar herniat.	Hyper-tension	–	house-wife	+	
5. T.N.	68	—	husb 960 cigs	father 400 cigs	older bro(LC) Yng(LC) sister	Injury rt. hand	—	+	plastic industry	–	
6. T.S.	79	—	husb +	—	Mother (GC) old.(LC) bro.	duodenal ulcer	Neuro-genic cystitis	+	house-wife	+	
7. K.N.	78	—	son 1,600 cigs	husb 450 cigs	father (GC)	appendic-hypo-tension	Parkins. angina pectoris	+	pawn-broker	+	

Table 1. (con't) B. Small cell carcinoma (women)

	Age	Active smoking	Passive smoking: Past	Passive smoking: Present	Familial cancer	Personal history of disease	Concomitant illness	Air pollution	Occupation	Stress	Others
1. K.Y.	67	350	son 100 cigs	—	mother (GC) old (RC) sister	uterus ca hepatit. gall stone	cardiac insuff.	—	housewife	+	
2. E.Y.	50	625	husb +	—	father (GC)	hysterec. gast.uld lymph node TB	—	+	family factory	+	
3. T.H.	70	500	husb + daught +	--	old bro (GC) yng bro (?C)	gall stone cere. embol	—	—	housewife	+	
4. F.M.	72	300	husb 370 cigs son 600 cigs	?	—	pul TB bronch. asthma	—	+	housewife	-	
5. T.T.	72	—	daughter cig[20 grand 550 child cigs	fath. 320 uncle 300 husb 640 cigs	yng sis (MC) yng (UC) sis	breast ca	—	—	teacher	+	divorced

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Table 2. Adenocarcinoma in women

A. Adenocarcinoma

	Age	Active smoking	Passive smoking: Past	Passive smoking: Present	Familial cancer	Personal history of disease	Concomitant illness	Air pollution	Occupation	Stress	Others
1. K.Y.	73	—	son +	mother pipe, husb 200 cigs	old sister (LC)	pleurisy	hypertension	+	camera store	—	
2. Y.M.	75	—	husb 1,040 cigs, son +	?	old bro (EC)	traffic accident	—	—	agricult.	—	
3. Y.M.	66	—	husb 700 cigs	father +	mother (CC)	uterine fibroid	hypertension, atr. fibril.	—	housewife	+	depression
4. T.M.	77	—	son 1,050 cigs	father +, husb 125 cigs	old sis (GC)	—	hypertension	—	housewife	—	
5. K.M.	71	—	husb 470 cigs	father- pipe, mother- pipe	mother (EC), old bro (LC)	hysterec., herpes	—	—	agricult.	—	
6. Y.T.	76	—	son 310 cigs	father +, grandparent 300	fath (RC), moth (GC)	fracture of vertebra	hypertension	—	agricult.	—	
7. S.W.	66	—	son 400 cigs	—	mother (EC), old brother (GC)	wrist fracture	—	furnace (soot)	fish market	±	
8. Y.F.	50	—	—	father 150, husb 200 cigs	grandfath (EC), aunt (GC)	uterine fibroid, hernia	—	—	housewife	—	
9. T.M.	60	—	husb 600, son 180 cigs	?	uncle (GC), aunt (LyC), MLy), child	—	rheumatism	—	housewife	+	
10. H.O.	49	—	+ at work	husb 480 cigs	cousin (GC), cousin (?C)	—	—	+	coffee shop	+	
11. H.Y.	64	—	husb 700 cigs	father pipe	mother (EC)	uterine fibroid, lung absc.	—	+	housewife	—	2
12. S.S.	68	—	son 580, son 100 cigs	husb 800, uncle 200, yng bro 180 cigs	—	—	hypertension	—	agricult.	—	husband: lung ca
13. T.I.	61	—	husb 800 cigs	fath 600 cigs	—	—	pulmonary TB	+	agricult.	—	pul (+) infection

the greatest influence was found to be that of present exposure, with a significant ($p < 0.05$) difference from the controls. Some differences were also seen in cases of all lung cancers and of adenocarcinoma who had history of passive smoking.

Among active smokers (Table 4), there was no difference between the lung cancer group and controls, but the combined number of cases of squamous cell carcinoma and small cell carcinoma was significantly ($p < 0.01$) higher in active smokers compared with non-active smokers, while the incidence of adenocarcinoma actually had a negative correlation with active smoking.

Among passive smokers (Table 4), when compared 1:1 with controls who were also non-active smokers, no significance was observed in the history of exposure, overall, present or past, but the ratio was virtually the same as that when active smokers were included (Table 3). Some difference, however, were observed for overall lung cancer and adenocarcinoma cases with history of past exposure to smoking.

When cumulative family incidence of cancer (Table 5) was investigated, it was found to create a significant ($p < 0.001$) difference between lung cancer cases and controls, the association being especially strong with adenocarcinoma, indicating that family incidence of cancer was an important factor in this type of cancer.

When smoking and familial cancer were combined (Table 5), the results were not significant with active smoking, but significant with passive smoking. The increase in risk when familial cancer and passive smoking were combined over that of familial history alone was as follows: All lung cancers + present exposure to passive smoking, x11.7; all lung cancers + past exposure to passive smoking, x 10.0; all lung cancers + active or passive smoking, x17.3; squamous cell carcinoma + small cell carcinoma + present exposure to passive smoking, x7.0; squamous cell carcinoma + small cell carcinoma + active or passive smoking, x40.8; and adenocarcinoma + past exposure to passive smoking, x26.7.

3. Discussion

The question of lung cancer development in non-smokers exposed over extended periods to smoking by others in the family and at the place of work has become a social concern not only in the United States but also in Japan.

In the present study, we gathered detailed information on the history of illness and family background in 25 cases of lung cancer in women, and investigated the relations among passive smoking, active smoking and familial incidence of cancer. The subjects were residents of Nara Prefecture, most of them housewives or women engaged in farming. The passive smokers in this study were all living with one or more smokers, therefore presumably exposed to passive smoking daily from at least

	Lung cancer in women	Squamous cell ca. + small cell ca.	Adenocarcinoma	Controls	Significance	Relative risk
Passive smoking (Total)	25/25 (100)			40/50 (80)	<0.05	13.2
		12/12 (100)		17/24 (71)	<0.1	10.7
			13/13 (100)	23/26 (88)	NS	—
Passive smoking (At present)	23/25 (92)			32/50 (64)	<0.05	6.5
		11/12 (92)		14/24 (58)	<0.1	7.9
			12/13 (91)	18/26 (69)	<0.1	5.3
Passive smoking (In the past)	16/22 (73)			20/44 (45)	<0.1	3.2
		6/11 (55)		9/22 (41)	NS	—
			10/11 (91)	11/22 (50)	<0.1	10.0
Passive smoking (In childhood)	13/22 (59)			20/44 (45)	NS	—
		4/11 (36)		9/22 (41)	NS	—
			8/11 (73)	11/22 (50)	NS	—

( ): %, NS: not significant

Table 3. Passive smoking and lung cancer in women (controlled study 1).

	Lung cancer in women	Squamous cell ca. + small cell ca.	Adenocarcinoma	Controls	Significance	Relative risk
Active smoking (+)	8/25 (32)			14/50 (28)	NS	—
		8/12 (67)		4/24 (17)	<0.01	10.0
			0/13 (0)	10/26 (38)	<0.05	0.06
Passive smoking (at present)	17/17 (100)			14/17 (82)	NS	—
		4/4 (100)		3/4 (75)	NS	—
			13/13 (100)	11/13 (85)	NS	—
Passive smoking (in the past)	16/17 (94)			17/17 (71)	NS	—
		4/4 (100)		3/4 (75)	NS	—
			12/13 (92)	9/13 (69)	NS	—
Passive smoking (in childhood)	13/15 (87)			7/15 (47)	<0.1	7.4
		3/4 (75)		2/4 (50)	NS	—
			10/11 (91)	5/11 (45)	<0.1	12.0

( ): %, NS: not significant

Table 4. Passive smoking and lung cancer in women (controlled study 2).

	Lung cancer in women	Squamous cell ca. + small cell ca.	Adenocarcinoma	Controls	Significance	Relative risk
Cumulative familial cancer	$\frac{18}{25}$ (72)			$\frac{13}{50}$ (26)	<0.001	7.3
		$\frac{7}{12}$ (58)		$\frac{7}{24}$ (29)	NS	—
			$\frac{11}{13}$ (85)	$\frac{6}{26}$ (23)	<0.001	18.3
Active smoking + familial cancer	$\frac{4}{25}$ (16)			$\frac{4}{50}$ (8)	NS	—
		$\frac{4}{12}$ (33)		$\frac{2}{24}$ (8)	NS	—
			$\frac{0}{13}$ (0)	$\frac{2}{26}$ (8)	NS	—
Passive smoking (at present) + familial cancer	$\frac{18}{25}$ (72)			$\frac{9}{50}$ (18)	<0.0001	11.7
		$\frac{7}{12}$ (58)		$\frac{4}{24}$ (17)	<0.05	7.0
			$\frac{10}{13}$ (77)	$\frac{5}{26}$ (19)	<0.001	14.0
Passive smoking (in the past) + familial cancer	$\frac{11}{22}$ (50)			$\frac{4}{44}$ (9)	<0.001	10.1
		$\frac{3}{11}$ (27)		$\frac{2}{22}$ (9)	NS	—
			$\frac{8}{11}$ (73)	$\frac{2}{22}$ (9)	<0.001	26.7
Active or passive smoking + familial cancer	$\frac{23}{25}$ (92)			$\frac{20}{50}$ (40)	<0.001	17.3
		$\frac{12}{12}$ (100)		$\frac{9}{24}$ (38)	<0.005	40.8
			$\frac{11}{13}$ (85)	$\frac{11}{26}$ (42)	<0.05	7.5

( ): %, NS: not significant

Table 5. Familial incidence of cancer and smoking in relationship to lung cancer in women (Controlled study 3).

the evening until the following morning.

It was found that present exposure to passive smoking was more influential than past exposure; that active smoking had a fairly marked effect on the development of squamous cell carcinoma or small cell carcinoma; and that in these histologic types, current (up to the present time) exposure to passive smoking had a marked effect. On the other hand, there was virtually no effect of active smoking on the development of adenocarcinoma,but there was suspicion of the effect of past or present exposure to smoking in this type of tumor.

The effect of passive smoking should be considered qualitatively and quantitatively. In assessing the qualitative effect of passive smoking, the following items should be considered: The amount of carcinogenic material in secondary smoke is greater than in the primary smoke[1]; when ten cigarettes are smoked in 1 hour, the level of COHb in the blood of the non-smoker rises to about the same concentration as that following the active smoking of one cigarette[2]; the amount of urinary nicotine of a non-smoker increases in parallel to the number of active smokers generating smoke, demonstrating a dose response effect[3];benzpyrene in the urine of a non-smoker exposed to smoke becomes detectable, and this amount decreases when the non-smoker avoids exposure to smoke[4]; upon exposure to smoking for 6 hours, the amount of mutagens in the urine of a non-smoker increases markedly[5]; and that mice and dogs exposed to smoke develop lung tumors[6]. These results suggest the possibility of lung carcinogenesis through passive smoking.

Quantitative assessment of passive smoking has been presented in the following findings: The increase in incidence of lung cancer in non-smoking wives of heavy cigarette smokers over that in non-smoking wives of non-smokers was x2.08 in Japan (Hirayama)[7], x3.4 in Greece (Trichopoulos)[9], x3.11 in the United States (Correa)[10], x1.94, also in the United States (Miller)[11], x12.78 in Kanagawa Prefecture (Inoue)[22] and x1.5-2.1 in Hiroshima and Nagasaki (Akiba)[23]. When the findings by Garfinkel (U.S.)[8] and Koo (Hong Kong)[17] are excluded, mortality of non-smoking wives from lung cancer seems to increase about two-fold. Increase in the risk of passive smoking in the family is especially marked in non-smoking women under 50 years of age, while habitual smokers are subject to both active and passive smoking[12]. Akiba[23] found that of women who are not exposed to either active or passive smoking, 100% develop either adenocarcinoma or large cell carcinoma; that the incidence of these tumors decreases to 84% in passive smokers and to 42% in active smokers; and that in the latter cases there is a proportional increase in squamous cell carcinoma and small cell carcinoma [23]. These are similar to our findings.

In these reports, however, there are no consistent results concerning significance or dose response, and there is no unified interpretation at this time.

Some of the explanations for the inconsistencies are the following: (1) Differences in the living environment, (2) lack of definite information on passive smoking before marriage, (3) differences between women who work outside and those who are self-employed, (4) duration of periods when husband and wife are together, (5) smoking habit of the husband and conditions in the home, (7) mealtime habits, (8) incidence of cancer in the family and (9) age when the cancer developed. The paucity of information on these matters has been pointed out[6,13]. The present study was a survey of the Nara region where most women who were the subjects of the investigation were self-employed. Information was gathered regarding the histologic type of tumor, time of exposure to smoking, and incidence of cancer in the family, and although the number of cases was small, a certain degree of control was exercised. Correa[10] studied the relation of lung cancer to past exposure to passive smoking, and concluded that the effect of smoking by the mother could be seen in male lung cancer patients but not in women lung cancer cases.

Extrinsic and intrinsic factors may interact in carcinogenesis. The leading extrinsic factor in lung cancer is presumably cigarette smoking, while genetic cancer may be an intrinsic factor. We investigated the history of relatives three times removed from the principal, and found that with adenocarcinoma there was a strong indication of association of familial incidence of cancer, while with squamous cell carcinoma and small cell carcinoma, association of familial incidence was seen but not to a significant degree in comparison with controls. The association, however, was observed in 4 out of 5 cases of small cell carcinoma while in squamous cell carcinoma there was more variability. There is need for further study in larger numbers of cases. In another investigation of familial factor, the risk of development of lung cancer when there has been a family incidence was 8-fold over cases without any familial occurrence of lung cancer in Kawasaki City, and 5.9-fold in Tokyo[18]. Aoki[19] also pointed out that the risk of cancer of many organs was 2-3 times higher in families which had cases of cancer than in families without such history.

Tokuhata[21], in a survey of 270 cases of lung cancer, assessed the risk when familial incidence and active smoking were combined, and found the following: Compared with individuals without either factor, the risk for the non-smoker with familial history was 3.96-fold; for the smoker without familial history it was 5.45-fold; and for the smoker with familial history it was 13.64-fold. He stated that when corrected for smoking habit, the risk for those with familial history was increased 2.5-fold, approximately the same level of risk as that of smoking and claimed that the two factors are synergistic.

In our present study, the findings indicated that compared with controls,

passive smoking, current or past, increased the risk for lung cancer when familial history was present. When the data were sorted according to histologic type of lung cancer, risk was increased for squamous cell carcinoma and small cell carcinoma when active or passive smoking was combined with familial history, while with adenocarcinoma the influence of familial history was considerable, and the effect of passive smoking in the past was suspected.

Since the number of cases was small and the amount of passive smoking could not be determined so that dose response could not be demonstrated, no definite conclusion could be drawn from the present study, but there was a suggestion that for women in the Nara region, passive smoking is associated with development of lung cancer in women. The effect of passive smoking which has continued to the present time was especially marked, particularly notable in squamous cell carcinoma and small cell carcinoma. With adenocarcinoma, the effect of passive smoking in the past was suspected.

Along with passive smoking, the association of some intrinsic factor (genetic tendency) to varying degrees in the different histologic types of lung cancer in women, especially in adenocarcinoma, was apparent.

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